

**NTP TECHNICAL REPORT**  
**ON THE**  
**TOXICOLOGY AND CARCINOGENESIS**  
**STUDIES OF**  
**LAURIC ACID DIETHANOLAMINE CONDENSATE**  
**(CAS NO. 120-40-1)**  
**IN F344/N RATS AND B6C3F<sub>1</sub> MICE**  
**(DERMAL STUDIES)**

**NATIONAL TOXICOLOGY PROGRAM**  
**P.O. Box 12233**  
**Research Triangle Park, NC 27709**

**July 1999**

**NTP TR 480**

**NIH Publication No. 99-3970**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
**National Institutes of Health**

## FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: <http://ntp-server.niehs.nih.gov>.

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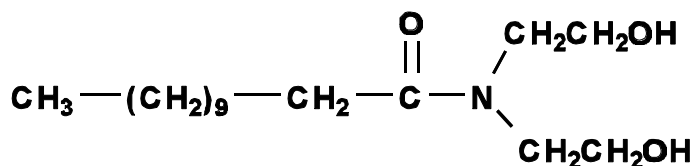
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## ABSTRACT



### LAURIC ACID DIETHANOLAMINE CONDENSATE

CAS No. 120-40-1

Chemical Formula:  $\text{C}_{16}\text{H}_{33}\text{NO}_3$  Molecular Weight: 287.50

**Synonyms:** N,N-bis(2-hydroxyethyl) dodecanamide; N,N-bis(hydroxyethyl) lauramide; N,N-bis(β-hydroxyethyl) lauramide; bis(2-hydroxyethyl) lauramide; coco diethanolamide; coconut oil amide of diethanolamine; diethanollauramide; N,N-diethanollauramide; N,N-diethanollauric acid amide; lauramide DEA; lauric diethanolamide; lauroyl diethanolamide; lauryl diethanolamide; LDA; LDE

**Trade names:** Clindrol 200 L; Ninol AA62; Onyxol 345; Rewomid DLMS; Rewomid DL 203/S; Richamide 6310; Rolamid CD; Standamid LD; Steinamid DL 203 S; Super amide L-9A; Super amide L-9C; Synotol L-60; Unamide J-56; Varamid ML 1

Lauric acid diethanolamine condensate is widely used in cosmetics, shampoos, soaps, and related consumer products, to which there is extensive human exposure. Because of the lack of information about potential risks associated with long-term exposure, lauric acid diethanolamine condensate, coconut oil acid diethanolamine condensate, and oleic acid diethanolamine condensate were selected as representative of the class of diethanolamides for evaluation of prechronic toxicity and carcinogenic potential. Male and female F344/N rats and B6C3F<sub>1</sub> mice were exposed to lauric acid diethanolamine condensate dermally for 14 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, and mouse peripheral blood erythrocytes.

#### 14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were administered 0, 25, 50, 100, 200, or 400 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 14 weeks. All animals

survived until study termination. Final mean body weights and body weight gains of males receiving 200 or 400 mg/kg were significantly less than those of the vehicle control group. Irritation of the skin at the site of application was observed in males receiving 100 mg/kg or greater and in females receiving 200 or 400 mg/kg. Kidney weights of females administered 200 or 400 mg/kg were significantly greater than those of the vehicle control group. There were dose-dependent increases in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, chronic inflammation, parakeratosis, and ulcer.

#### 14-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were administered 0, 50, 100, 200, 400, or 800 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 14 weeks. All animals survived until the end of the study, and final mean body weights and body weight gains of dosed mice were generally similar to those of the vehicle control

groups. Irritation of the skin at the site of application was observed in all males and females administered 400 or 800 mg/kg. The kidney weights of males receiving 100, 400, or 800 mg/kg and females receiving 800 mg/kg were significantly greater than those of the vehicle controls. Liver weights of females administered 200 mg/kg or greater were significantly greater than those of vehicle controls. Increased incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, chronic inflammation, parakeratosis, and ulcer, were observed in males and females receiving 200 mg/kg or greater.

## 2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were administered 0, 50, or 100 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 104 or 105 weeks.

### *Survival and Body Weights*

There were no significant differences between vehicle control and dosed males or females in survival or mean body weights.

### *Pathology Findings*

There were no chemical-related differences in neoplasm incidences. Dose-related increases occurred in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, hyperkeratosis, chronic inflammation, parakeratosis, and ulcer.

## 2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were administered 0, 100, or 200 mg lauric acid diethanolamine condensate/kg body weight in ethanol by dermal application for 105 or 106 weeks.

### *Survival and Body Weights*

There were no significant differences in survival between vehicle control and dosed males or females. Mean body weights of females that received 200 mg/kg were less than those of the vehicle controls beginning at week 33.

### *Pathology Findings*

The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in dosed females compared to the vehicle controls, as was the incidence of hepatocellular adenoma in the 100 mg/kg female group. There were dose-related increases in the incidences of nonneoplastic lesions of the skin at the site of application, including epidermal and sebaceous gland hyperplasia, hyperkeratosis, chronic inflammation, and parakeratosis. Dosed males had greater incidences of thyroid gland follicular cell focal hyperplasia than did the vehicle controls.

## GENETIC TOXICOLOGY

Lauric acid diethanolamine condensate was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, or TA1535, with or without S9 metabolic activation enzymes. No increase in the frequency of mutant colonies of L5178Y mouse lymphoma cells was noted after exposure to lauric acid diethanolamine condensate, with or without S9. In cytogenetic tests with cultured Chinese hamster ovary cells, lauric acid diethanolamine condensate was shown to induce sister chromatid exchanges, but not chromosomal aberrations, with and without S9. *In vivo*, no increase in the frequency of micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male and female mice treated dermally with lauric acid diethanolamine condensate for 14 weeks.

## CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity\** of lauric acid diethanolamine condensate in male or female F344/N rats administered 50 or 100 mg/kg or in male B6C3F<sub>1</sub> mice administered 100 or 200 mg/kg. There was *some evidence of carcinogenic activity* in female B6C3F<sub>1</sub> mice based on increased incidences of hepatocellular neoplasms. These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate.

Dermal administration of lauric acid diethanolamine condensate to rats and mice for 2 years resulted in increased incidences of epidermal and sebaceous

gland hyperplasia, hyperkeratosis, chronic inflammation, and parakeratosis at the site of application. Lauric acid diethanolamine condensate administration

also resulted in increased incidences of thyroid gland follicular cell hyperplasia in dosed male mice.

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\* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

**Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies  
of Lauric Acid Diethanolamine Condensate**

	Male F344/N Rats	Female F344/N Rats	Male B6C3F <sub>1</sub> Mice	Female B6C3F <sub>1</sub> Mice
<b>Doses in ethanol by dermal application</b>	0, 50, or 100 mg/kg	0, 50, or 100 mg/kg	0, 100, or 200 mg/kg	0, 100, or 200 mg/kg
<b>Body weights</b>	Dosed groups similar to vehicle control group	Dosed groups similar to vehicle control group	Dosed groups similar to vehicle control group	200 mg/kg group less than vehicle control group
<b>Survival rates</b>	12/50, 18/50, 16/50	28/50, 26/50, 22/50	40/50, 37/50, 41/50	37/50, 40/49, 29/50
<b>Nonneoplastic effects</b>	<u>Skin (site of application):</u> epidermal hyperplasia (0/50, 29/50, 44/50); sebaceous gland hyperplasia (0/50, 27/50, 44/50); hyperkeratosis (0/50, 23/50, 25/50); chronic inflammation (0/50, 10/50, 28/50); parakeratosis (0/50, 21/50, 33/50); ulcer (0/50, 4/50, 25/50)	<u>Skin (site of application):</u> epidermal hyperplasia (5/50, 33/50, 44/50); sebaceous gland hyperplasia (3/50, 41/50, 45/50); hyperkeratosis (0/50, 20/50, 29/50); chronic inflammation (3/50, 35/50, 34/50); parakeratosis (2/50, 12/50, 25/50); ulcer (3/50, 2/50, 10/50)	<u>Skin (site of application):</u> epidermal hyperplasia (4/50, 45/50, 50/50); sebaceous gland hyperplasia (1/50 45/50, 48/50); hyperkeratosis (3/50, 45/50, 49/50); chronic inflammation (1/50, 13/50, 28/50); parakeratosis (0/50, 1/50, 5/50)  <u>Thyroid gland:</u> follicular cell hyperplasia (18/50, 24/50, 36/50)	<u>Skin (site of application):</u> epidermal hyperplasia (0/50, 42/49, 50/50); sebaceous gland hyperplasia (0/50, 43/49, 45/50); hyperkeratosis (4/50, 41/49, 48/50); chronic inflammation (0/50, 24/49, 40/50); parakeratosis (0/50, 3/49, 9/50)
<b>Neoplastic effects</b>	None	None	None	<u>Liver:</u> hepatocellular adenoma (23/50, 32/49, 29/50); hepatocellular adenoma or carcinoma (combined) (28/50, 40/49, 36/50)
<b>Level of evidence of carcinogenic activity</b>	No evidence	No evidence	No evidence	Some evidence
<b>Genetic toxicology</b>				
<i>Salmonella typhimurium</i> gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9			
Mouse lymphoma gene mutations:	Negative with and without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells <i>in vitro</i> :	Positive with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells <i>in vitro</i> :	Negative with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood <i>in vivo</i> :	Negative			

## EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

## NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on lauric acid diethanolamine condensate on 9 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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## SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 9 December 1997, the draft Technical Report on the toxicology and carcinogenicity studies of lauric acid diethanolamine condensate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of lauric acid diethanolamine condensate by discussing the uses of the chemical and the rationale for conducting the studies, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms in female mice and non-neoplastic lesions in male and female rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male and female F344/N rats and male B6C3F<sub>1</sub> mice and *some evidence of carcinogenic activity* in female B6C3F<sub>1</sub> mice.

Dr. Hecht, a principal reviewer, agreed with the proposed conclusions. As in the case of the Technical Report on coconut oil acid diethanolamine condensate, he felt that the scientific conclusions were clouded by the use of a mixture with such a large amount of diethanolamine as a contaminant, uncertainty about the actual concentration of the nitrosodiethanolamine impurity, and the confounding issue of the considerable spontaneous incidence of mouse liver neoplasms.

Dr. Goldsworthy, the second principal reviewer, agreed with the proposed conclusions with the provision that the last sentence of the conclusions for carcinogenicity be amended to indicate the association

of the neoplasms with the free diethanolamine in the condensate.

Dr. Bailer, the third principal reviewer, agreed with the proposed conclusions. He said he had some specific questions relating to the logistic model used such as whether the fit had been quantified, why the comparisons were made using survival, and what was the sensitivity of the model to the assumed amounts of diethanolamine in the various condensates. Dr. J.K. Haseman, NIEHS, said he would consider adding a goodness of fit statistic or a graphical display to the relevant table which would show how well the predicted and observed values agreed (Figure 5, page 47). Dr. Bailer noted many organ/tissue sites outlined in the text with trend test P values of 0.03 to 0.07 and wondered how it was decided which trends should be highlighted. He noted especially Zymbal's gland neoplasms in male rats for which he thought the findings might support *equivocal evidence*. Dr. J.R. Hailey, NIEHS, responded that in the case of the Zymbal's gland, one of the three neoplasms reported was determined not to be of Zymbal's gland origin. Dr. Irwin said that biological plausibility or meaningfulness also comes into consideration with borderline cases.

Dr. Goldsworthy moved that the Technical Report on lauric acid diethanolamine condensate be accepted with the revisions discussed and the conclusions as written, *no evidence of carcinogenic activity* in male and female rats and male mice, and *some evidence of carcinogenic activity* in female mice. The last sentence of the conclusions for carcinogenicity would be changed, as for the coconut oil acid diethanolamine condensate Technical Report, to read: "These increases were associated with free diethanolamine, which was present as a contaminant of lauric acid diethanolamine condensate." Dr. Bailer seconded the motion, which was accepted by seven votes with one abstention (Dr. Bus).